VOTRIENT™ (PAZOPANIB)

PEDIATRIC ONCOLOGY ADVISORY COMMITTEE MEETING

BRIEFING DOCUMENT

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TABLE OF CONTENTS

PAGE

1. EXECUTIVE SUMMARY

Pazopanib is an oral small molecule angiogenesis inhibitor that was approved by the FDA for treatment of advanced renal cell carcinoma in 2009 and is being studied in additional indications in adults, including adjuvant renal cell carcinoma, advanced soft tissue sarcoma and ovarian cancer. In 2009 a Phase I trial of monotherapy in pediatrics was begun in collaboration with the Children's Oncology Group (COG) to define the maximum tolerated dose (MTD), study an oral suspension formulation and investigate pharmacodynamic effects in subjects with soft tissue sarcoma (STS). The first part of this study is complete and determined an MTD of 450mg/m^2 QD. Pazopanib is generally well tolerated in children, but findings in juvenile toxicity studies identified effects on organ development in preweanling rats that preclude the use of pazopanib in children under age 2. Juvenile toxicity studies in rats also identified effects on bone and teeth that could occur in children. A Phase II study in pediatrics in collaboration with COG is expected to begin enrollment in 2012. In 2010 GSK and the European Medicines Agency (EMA) agreed to a Pediatric Investigation Plan (PIP) that includes juvenile toxicity studies, development of an age appropriate formulation, a Phase I study to assess safety and determine the MTD of monotherapy and Phase II and III studies of monotherapy in rhabdomyosarcoma (RMS), non-RMS STS and Ewing family sarcomas. The small number of pediatric subjects available for clinical trials, and the existing toxicologic concerns have been challenges in the development of pazopanib in pediatrics.

2. PAZOPANIB REGULATORY HISTORY

Pazopanib (*5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride*) is an orally available selective, small molecule ATP competitive inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3 with IC_{50} values of 10, 30 and 47 nM, respectively. Pazopanib also inhibits the platelet-derived growth factor (PDGF) receptors α and β, stem cell factor receptor (CD-117 or c-Kit), fibroblast growth factor (FGF) receptors 1 and 3, and macrophage colony stimulating factor receptor (c-fms) [Harris, 2008] .

Tumors depend upon new vasculature for provision of oxygen and nutrients and produce signals to promote angiogenesis. Many angiogenic factors, including VEGF, PDGF, FGF, transforming growth factor-β, and tumor necrosis factor-α have been identified. A number of anti-angiogenic strategies to treat cancer have been tested, including inhibitors of angiogenic factor signaling (e.g., VEGFR inhibitors), disruption of existing tumor vasculature, and inhibition of angiogenic factor release. Several anti-angiogenic agents have received regulatory approval for treating specific cancers.

Pazopanib has received regulatory approval for the treatment of advanced renal cell carcinoma (RCC) under the trademark Votrient™ in a number of countries worldwide including the US (19 October 2009) and the EU (14 June 2010) . Marketing applications have been filed and are under review in the US, EU and other countries for pazopanib for the treatment of advance STS (excluding gastrointestinal stromal tumors and adipocytic sarcoma) following prior chemotherapy.

FDA waived pediatric study requirements for advanced RCC because the disease/condition does not exist in children and therefore the necessary studies are impossible or highly impractical.

In 2008 the European Medicines Agency confirmed that the class waiver regarding pediatric development for products intended to treat kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, and renal medullary carcinoma and rhabdoid carcinoma of the kidney) for the RCC indication was applicable to pazopanib.

In 2010, a Pediatric Investigation Plan (PIP) in Soft Tissue Sarcoma (STS) was approved by the European Medicines Agency. The approved PIP is a commitment to study pazopanib in children and adolescents with advanced STS, including rhabdomyosarcoma and Ewing family sarcomas. Although there have been no formal interactions with the FDA to date regarding pediatric development of pazopanib, GSK does intend to discuss pediatric development plans with the FDA in appropriate indications. A Phase I trial in pediatric patients is currently ongoing.

3. CLINICAL DEVELOPMENT OF PAZOPANIB IN ADULTS IN CANCER INDICATIONS

3.1. Pharmacokinetics in adults

Pazopanib pharmacokinetics in adults were evaluated in the monotherapy Phase I trial [Hurwitz, 2009]. The oral bioavailability of pazopanib reflects absorption that is limited by solubility above doses of 800 mg once daily Increases in doses above 800 mg, up to the highest dose evaluated (2000 mg), in the fasted state did not increase systemic exposure. The mean half-life was 30.9 hours in the 800 mg once daily dose group, the monotherapy dose selected for administration in adult Phase II and Phase III clinical trials. Oral absorption is significantly enhanced when dosed with food [Heath, 2010]. The low absolute bioavailability of pazopanib (median 21%) suggests that the majority of the oral dose recovered unchanged in feces (67%) represents unabsorbed drug. Pazopanib is not extensively metabolized and first-pass metabolism is minor, consistent with its low plasma clearance and small volume of distribution. Pazopanib that is metabolized is primarily CYP3A4-dependent and systemic exposure to pazopanib is altered by inhibitors and inducers of this enzyme [Goh, 2010]. Renal impairment is unlikely to alter systemic exposure significantly.

3.2. Pharmacodynamics in Adults

Pazopanib, at a monotherapy dose of 800 mg once daily, resulted in increased circulating VEGF and decreased soluble VEGFR-2 in human adults, consistent with inhibition of VEGF receptors [Hurwitz, 2009]. Concentration-effect relationships were observed between trough plasma pazopanib concentrations and increased blood pressure in the First Time in Human study (Study VEG10003) and the percent change from baseline in soluble VEGFR-2 nadir in the Phase II study in RCC (Study VEG102616) [Hutson, 2010]. The trough plasma pazopanib concentrations associated with one-half the maximal effect (EC_{50}) in both concentration-effect relationships were similar (21.3

µg/mL for sVEGFR2 and 15.3 µg/mL for increased blood pressure) and demonstrate that there is a consistent inhibition of VEGF receptor(s) in subjects with cancer when plasma pazopanib concentrations are maintained above 15 µg/mL.

3.3. Biomarker and pharmacogenomic studies in adults

Plasma levels of cytokines and angiogenic factors and pharmacogenomic markers have been studied in adult subjects with advanced RCC to identify markers predictive of benefit from pazopanib treatment. Plasma levels of IL8, OPN and TIMP1 were prognostic for progression-free survival (PFS) in the Phase III trial in RCC [Liu, 2011]. Subjects with high plasma levels of IL6 had a greater PFS benefit from pazopanib treatment than subjects with low levels. Although high IL6 levels have some predictive value, they cannot be used for patient selection because subjects with low IL6 levels also had increased PFS in the pazopanib arm compared with placebo. Polymorphisms in the IL8 and HIF1A genes correlated with PFS in pazopanib treated subjects with advanced RCC [Xu, 2011a]. Whether these markers are predictive or prognostic is not certain, because the control group (i.e., subjects from the placebo arm who did not receive pazopanib upon progression) was small. No markers predictive for overall survival in pazopanib treated subjects with advanced RCC have been identified.

Pharmacogenomic studies have also been conducted to identify markers that predict adverse events. Increased bilirubin in pazopanib treated subjects with RCC is associated with the Gilbert's syndrome polymorphism in the UGT1A1 gene [Xu, 2010]. Polymorphisms in the HFE gene are associated with increases in ALT in pazopanib treated subjects with RCC [Xu, 2011b].

3.4. Combination therapy with pazopanib

Combination of pazopanib with conventional chemotherapy or other targeted agents has generally led to increased toxicity. For many combinations it has not been possible to achieve a dose of pazopanib that is both tolerable and results in adequate target engagement. A summary of the findings of completed Phase I combination studies with pazopanib is shown in Table 1.

Table 1 Completed Pazopanib Combination Studies in Adult Subjects

Combination Regimen	Maximum Tolerated Doses	Potential Limitations to Further Development
Pazopanib + Paclitaxel [Tan, 2010]	Pazopanib 800 mg daily + Paclitaxel 80 mg/m^2 on Days 1, 8 and 15 every 28 days.	None
Pazopanib + Paclitaxel + Carboplatin	Pazopanib 200 mg daily + Paclitaxel 175mg/ m^2 and Carboplatin AUC 5 Q 21 days.	24-38% dose reductions 77% dose interruptions Cumulative fatigue and cytopenias
Pazopanib + FOLFOX	Pazopanib 800 mg daily + full dose FOLFOX 6	70-93% dose interruptions 50-71% dose reductions Neutropenia
Pazopanib + CapeOX	Pazopanib 800 mg QD + Capecitabine 850 mg/ m^2 BID days 1-14 + Oxaliplatin 130 mg/ m^2 Q 21 days	43-71% interruptions 14-43% dose reductions Cumulative hand foot syndrome
Pazopanib + Lapatinib [Dejong, 2006]	Pazopanib 800 + Lapatinib 1500 Pazopanib 400 + Lapatinib 1000	Diarrhea, LFT increase
Pazopanib + Premetrexed	Pazopanib 800 mg QD + Premetrexed 500 mg/ m^2 every 21 days	33% dose reduction 47% interruptions >50% Grade 4 neutropenia

3.5. Current Drug Development Plan for Indications in Adults

3.5.1. RCC

3.5.1.1. Advanced RCC

Pazopanib was approved for treatment of advanced RCC in the US, EU and many other countries based on the results of VEG105192, a double-blind, randomized, placebo-controlled Phase III trial. There was a statistically significant improvement in the primary endpoint of PFS in the pazopanib-treated subjects compared to placebo-treated subjects (hazard ratio [HR] 0.46, 95% CI 0.34 to 0.62, p< 0.0000001). The median PFS in the pazopanib arm was more than double that in the placebo arm: 9.2 months (95% CI, 7.4, 12.9) versus 4.2 months (95% CI, 2.8, 4.2), respectively. The robustness of the primary analysis of PFS was confirmed by multiple sensitivity analyses [Sternberg, 2010].

Overall survival was not statistically different between the pazopanib arm and the placebo arm (HR = 0.91, stratified log-rank p-value, 0.224). Subjects who progressed on the placebo arm were eligible to receive pazopanib through an open-label extension study (VEG107769) at the discretion of the subject and the investigator, provided the subject

met the eligibility criteria. Of note, 54% of subjects in the placebo arm received pazopanib, many starting early in the study, and an additional 12% received other systemic therapies. Sixty six percent of subjects in the placebo arm and 30% of subjects in the pazopanib arm received post-disease progression therapy. Imbalances in post disease progression treatment confounded the OS analyses.

3.5.1.2. Adjuvant therapy for high risk RCC

Pazopanib is also being studied as adjuvant therapy for high risk RCC that has been completely resected, in a randomized, double-blind, placebo-controlled Phase III trial (VEG113887).

3.5.2. Soft Tissue Sarcoma

Pazopanib has been studied in advanced STS following prior chemotherapy (subjects with gastrointestinal stromal tumors or adipocytic tumors were excluded). A Phase III, randomized, double-blind, placebo-controlled trial (VEG110727), showed an improvement in PFS in the pazopanib arm compared with the placebo arm [Van Der Graaf, 2011]. The median PFS in the placebo arm was 7.0 weeks (95% CI: 4.4, 8.1) and in the pazopanib arm was 20.0 weeks (95% CI: 17.9, 21.3), with a corresponding hazard ratio (HR) of 0.35 (95% CI: 0.26, 0.48, $p<0.001$) as assessed by the independent radiologist. Interim overall survival (OS) data showed a median OS for the pazopanib treated arm of 11.9 months and 10.4 months for the placebo arm. The HR was 0.82 and was not statistically significant ($p=0.156$)

3.5.3. Ovarian cancer

Pazopanib is being studied in a randomized, double-blind, placebo-controlled Phase III trial to evaluate the efficacy and safety of pazopanib monotherapy versus placebo in women who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer.

3.5.4. Other tumor types investigated in adults

Pazopanib, given either as monotherapy or combination therapy, has also been investigated in other tumor types including non-small cell lung cancer [Altorki, 2010], breast cancer [Taylor, 2010], thyroid cancer [Bible, 2010], cervical cancer [Monk, 2010], glioblastoma multiforme [Iwamoto, 2010], and bladder cancer [Necchi, 2011; Pili, 2011].

3.6. Safety of pazopanib administered to adults

The most common adverse reactions (≥ 20 %) observed in subjects with advanced RCC treated with pazopanib are diarrhea, hypertension, hair color changes, nausea, anorexia and vomiting. Warnings and precautions in the prescribing information for pazopanib are hepatotoxicity, prolonged QT interval and torsades de pointes, fatal hemorrhage, arterial thrombotic events, gastrointestinal perforation or fistula, hypertension, hypothyroidism and proteinuria. Temporary interruption of pazopanib is recommended in patients undergoing surgical procedures. Pazopanib can cause fetal harm when administered to pregnant women.

The overall safety profile of pazopanib in adult STS studies was similar to the profile described in the RCC prescribing information for Votrient™ (pazopanib) [VOTRIENT, 2010]. Myocardial dysfunction was more common in the Phase III STS study, in which almost all subjects had received prior anthracycline therapy. Two new safety signals were identified in the STS studies: increased rates of venous thromboembolism (5% all grades in the pazopanib arm compared with 2% all grades in the placebo arm) and pneumothorax (3% all grades in the pazopanib arm compared with <1% all grades in the placebo arm).

4. CLINICAL DEVELOPMENT OF PAZOPANIB IN PEDIATRICS

4.1. Introduction and background

The focus of pazopanib development in pediatrics is STS, including rhabdomyosarcoma and Ewing family sarcomas. Although sarcomas are most common in patients over the age of 50 years, approximately 10% of patients diagnosed with sarcoma are children. Sarcomas account for 15% to 20% of pediatric cancers, but only about 1% of adult cancers. The most common sarcomas in pediatric patients are rhabdomyosarcoma (RMS), Ewing sarcoma and osteosarcoma. Based on clinical activity seen in the Phase I monotherapy trial or scientific rationale, other tumor types may also be studied.

4.2. Role of VEGF in organ development

VEGF signaling plays an important role in vascular development and hematopoiesis as well as vasculogenesis during organ development. Inactivation of VEGF in newborn mice results in increased mortality and impaired organ development in the liver and kidney by interference with endothelial cell survival, but this effect was much less significant as the animals matured with virtually no effects after postnatal day 28 [Gerber, 1999a]. VEGF has been shown in murine gene targeting experiments to be required for development and maintenance of the glomerular filtration barrier.

In infants and toddlers (1 to 24 months), children (2 to 11 years) and adolescents (12 to 18 years) there is the potential for growth velocity to be impaired. VEGF inhibitors suppress endochondral bone formation in young mice, a fundamental mechanism for longitudinal bone growth [Gerber, 1999b]. In humans at approximately age 17 years, and at the stage when final height is determined, the cartilage cells stop duplicating so that when skeletal maturity is reached at the age of 18-25 years, all of the cartilage will have been replaced by bone. The effect on bone growth in adult rodents by an antiangiogenic agent is reversible after two weeks cessation of the treatment.

VEGF is essential for the development of corpus luteum and therefore its inhibition has been reported to induce ovarian atrophy and reduce corpora lutea.

4.3. Nonclinical studies

4.3.1. Juvenile toxicity studies

Preclinical pazopanib toxicology studies originally conducted in young, sexually mature rats aged 10-12 weeks at study start for the initial indication of renal cell carcinoma, identified bone (hypertrophy of epiphyseal growth plates) and teeth (effects on dentition including excessively long, brittle, broken and/or missing teeth and dentine and enamel degeneration and thinning) as key target organs. These effects were pharmacologically mediated due to VEGFR inhibition and or disruption of the VEGF signaling pathway. Therefore, in addition to the toxicity profile described for adults it is expected that additional side effects in bone and teeth specific to the developing child will occur when treated with pazopanib. Juvenile toxicity studies were performed in pre- and post weanling rats to support the administration of pazopanib to pediatric subjects.

In an initial tolerability and toxicokinetic study, preweanling rats treated from postnatal day (PND) 9 to PND 25 did not tolerate a dose 30 mg/kg/day. Pazopanib caused mortalities and delayed organ growth and maturation of the kidneys, lungs, liver and heart, at a dose approximately 0.1 times the clinical exposure, indicating an age specific sensitivity to VEGF inhibition. Based on these data and the equivalent ages for organ maturation of these major organ systems in pediatric humans, GSK has recommended that subjects enrolled into pediatric clinical trials with pazopanib be at least 2 years of age.

The study in preweanling rats was followed by a definitive juvenile toxicity study dosing from PND 21 to PND 62 which included histopathology, clinical pathology, organ weights and other parameters. In this study findings were similar to those observed in adult rats at comparable exposures. Changes were seen in bone, trachea, teeth, adrenal, pancreas, stomach, duodenum, lymph node, male mammary gland and reproductive organs. Physeal hypertrophy was fully reversible after 4 weeks, but some animals showed evidence of physeal closure at the end of the off dose period. From these data, and as noted above, the growing bones, teeth and developing reproductive organs in human pediatric subjects may be particularly sensitive to pazopanib treatment as compared to adults. The effects on bone may be of greater concern in pediatric subjects, especially where an antiangiogenic agent is in chronic use.

4.3.2. Preclinical efficacy studies in pediatric tumors

The NCI-supported Pediatric Preclinical Testing Program (PPTP) performed Stage 1 testing of pazopanib *in vivo* against a subset of 7 childhood sarcoma xenograft models. Two Ewing cell lines, 4 alveoloar RMS cell lines, and 1 embryonal RMS cell line were tested. Pazopanib (100 mg/kg/day free base equivalent) was evaluated over a 28 day period with an additional two-week observation period. Both daily and twice-daily schedules have demonstrated anti-angiogenic activity against adult cancer xenografts. Pazopanib was well tolerated with no toxicity observed. All 7 tumor xenograft models tested were considered evaluable. Pazopanib induced significant differences in event-free survival (quadrupling of tumor volume from the initial tumor volume) distribution compared to controls in 4 (2 Ewing lines, 1 alveolar RMS, 1 embryonal RMS) of 7

sarcoma xenografts tested**.** Objective responses were not observed and no xenografts showed a shift in their median time to event ratio of greater than 2 (i.e., event-free survival Treated/Control > 2).

The study was repeated to test pazopanib at a higher total daily dose (100 mg/kg administered twice daily). Pazopanib was relatively well tolerated using the twice-daily dosing schedule. However, it showed no better activity with twice-daily dosing than had been demonstrated with daily dosing. The reason for the low level of activity despite twice daily dosing is not clear. GSK requested that the PPTP conduct a pharmacokinetic study to be certain that adequate exposures had been obtained. The concentration data generated by PPTP was similar to the mouse pharmacokinetic data GSK has established in other studies thus ruling out a possible discrepancy in exposure.

Other multikinase angiogenesis inhibitors have also demonstrated activity in preclinical models of pediatric tumors. Inhibition of the PDGF receptor by imatinib is effective in preclinical models of osteosarcoma [McGary, 2002]. VEGF or VEGR inhibition with monoclonal antibodies or small molecules impaired growth of Ewing sarcoma and rhabdomyosarcoma cell lines in in vivo models, but these studies are difficult to compare directly to the pazopanib preclinical experiments [Dalal, 2005; Gerber, 2000]. Multikinase angiogenesis inhibitors and VEGF antibodies have been effective in preclinical models of neuroblastoma [Rossler, 2008].

4.4. Studies of angiogenesis inhibitors in pediatric populations

The VEGF inhibitors bevacizumab, sunitinib, sorafenib and cediranib have been studied in pediatric subjects in Phase I trials. The data from these trials are informative with regard to effects of the class of angiogenesis and multikinase inhibitors used in pediatric populations, especially safety.

In the Phase 1 trial of bevacizumab monotherapy in pediatrics no dose limiting toxicities were observed, similar to the adult studies, and no maximum tolerated dose was defined for pediatric subjects [Glade Bender, 2008]. Three subjects had open epiphyses and complete radiographic evaluation. None showed physeal expansion after 1-2 months of therapy. Several studies of bevacizumab given in combination in pediatric subjects have been reported. Bevacizumab at 15 mg/m^2 q3 week was given in combination with vincristine, topotecan and cyclophosphamide in 7 subjects with first relapse of Ewing sarcoma [Leavey, 2010]. Six subjects were evaluable and none had a dose limiting toxicity. Five subjects had either a CR or SD. Bevacizumab at a dose of 10 mg/m^2 q2 weeks was studied in children with malignant glioma or diffuse brain stem glioma in combination with irinotecan [Gururangan, 2010]. The regimen had minimal efficacy.

In the Phase I sunitinib monotherapy study, reversible Grade 2 systolic dysfunction occurred in 1 subject in the first dose level and one subject in the -1 dose level [DuBois, 2011]. The protocol was amended to exclude subjects with prior anthracycline therapy or cardiac radiation exposure. No further cardiac toxicity was seen. The MTD was lower than the approved adult dose. Neutropenia, thrombocytopenia and transaminase elevations were the most commonly reported toxicities. Sunitinib was studied in seven subjects age 10-17 with advanced gastrointestinal stromal tumor (GIST) following failure

of imatinib [Janeway, 2009]. Subjects were treated at doses of 25, 37.5 or 50 mg QD for 4 weeks followed by 2 weeks off of therapy. Treatment had acceptable tolerability. One subject had a PR and 5 had SD.

In the sorafenib monotherapy phase I trial the MTD in children with solid tumors was 200 mg/m^2 BID, similar to the adult dose of 400 mg BID [Widemann, 2009]. DLTs were hyponatremia and hand foot syndrome. A Phase I study of sorafenib given in combination with clofarabine and cytarabine in relapsed or refractory leukemia has also been reported [Inaba, 2011]. Twelve subjects were treated, age 6 to 17 years. The MTD was 150 mg/m^2 BID and the dose limiting toxicities were rash and hand foot syndrome. Six subjects had a CR, 2 had a CR with incomplete blood count recovery and 1 had a PR.

The Phase I monotherapy trial of cediranib in pediatric subjects defined the MTD as 12 mg/m^2/day, which provided equivalent exposure to the adult fixed dose of 20 mg QD [Fox, 2010]. Dose limiting toxicities were nausea and fatigue. A subject with Ewing sarcoma and a subject with synovial sarcoma had PRs by WHO criteria. A subject with synovial sarcoma and a subject with osteosarcoma had minor responses by WHO criteria.

4.5. Pediatric formulation of pazopanib

Studies of an oral suspension of pazopanib in adults revealed that it has a strong bitter taste and unpleasant mouth -feel. The first generation of pazopanib powder for oral suspension (POS) is reconstituted with a 3:1 mixture of a commercially available syrup and water (mixed berry flavor) to counteract the bitter taste and poor mouth-feel characteristics. This formulation is being tested in Phase 1. Because the syrup is not available worldwide a second generation POS with the appropriate taste and mouth-feel masking characteristics is being developed that can be reconstituted with water.

4.6. Completed, ongoing and planned studies relevant to development of pazopanib in pediatric indications

A total of 4 studies relevant to pazopanib pediatric development have been completed, are on-going or are planned. They are listed in Table 2 and described in more detail below.

Table 2 Studies relevant to pediatric development of pazopanib

Study No.	Study Title	Study status	Endpoints
VEG10005	Adult suspension cohort within an open-label, two- period, randomized, crossover study to evaluate the effect of food on the pharmacokinetics of single doses of pazopanib in cancer subjects.	Completed	Relative bioavailability of suspension versus whole tablet in single dosing in adults
Children's Oncology Group Study ADVL0815	Phase I Pediatric Dose Finding Study for pazopanib monotherapy administered by tablet or oral suspension.	Currently recruiting	Determine the MTD for whole tablet and oral suspension.
Children's Oncology Group Study ADVL092X	Phase II stratified study to explore the efficacy of pazopanib monotherapy.	Planned	Clinical activity in Simon 2-stage design.
Pediatric Pazopanib Phase III trial	Phase III open-label, randomized trial to assess overall survival of children treated with pazopanib compared to physician's choice of therapy.	Planned-Contingent on positive results from Phase II trial	Overall survival.

4.6.1. VEG10005 (Completed)

VEG10005 was an open-label, two-period, randomized, crossover study, to evaluate the effect of food on the pharmacokinetics of single doses of pazopanib in adult cancer subjects [Heath, 2011]. One of the primary objectives was to evaluate the effect of an oral suspension dosing formulation on the PK of pazopanib in adult cancer subjects. Administration of a single dose of pazopanib 400 mg as a suspension increased AUC(0-72) by 33% and Cmax by approximately 29% and decreased Tmax by approximately 1 hour compared to administration of the whole tablet. These results indicate that administration of pazopanib 400 mg as a suspension increases the rate and extent of oral absorption relative to administration of the whole tablet.

4.6.2. ADVL0815 (On-going)

ADVL0815 is a Phase 1 study of pazopanib monotherapy in children with relapsed or refractory solid tumors conducted by the Children's Oncology Group Phase 1 Consortium. The primary objectives of the study are to estimate the maximum tolerated dose of oral pazopanib monotherapy, to define and describe the toxicities of oral pazopanib administered as either a tablet or suspension, and to characterize the pharmacokinetics of oral pazopanib in children with refractory solid tumors. Secondary objectives include a preliminary assessment of the antitumor activity of oral pazopanib, an assessment of the biological activity of oral pazopanib, and an exploration of concentration-effect relationships with biomarkers and clinical outcomes. The study has 3 parts. Part 1 is the dose escalation phase to determine the MTD of the tablet formulation. Part 2a is an expanded cohort to obtain pharmacokinetic data using pazopanib powder in suspension and Part 2b is an expanded cohort for subjects with soft tissue sarcoma to obtain imaging data using DCE-MRI.

Part 1 of the study used a rolling 6 design and is complete [Glade Bender, 2011]. The starting dose of pazopanib in Part 1 was 275 mg/m^2/day, approximately 60% of the adult dose of 800 mg QD. Twenty five eligible subjects enrolled between July 2009 and April 2010, with a median age of 13.4 years. The MTD was determined to be 450 mg/m^2, which provides an exposure similar to the adult dose of 800 mg QD. Two of 5 subjects treated at 600 mg/m^2 had DLTs (1 hypertension and 1 amylase increase). One of six evaluable subjects treated at the 275 mg/m^2 dose level had a DLT (increased lipase) and 1of 6 evaluable subjects treated at the 450 mg/m^2 dose level had 2 DLTs (hypertension and proteinuria). None of the 6 subjects treated at the 350 mg/m^2 dose level had a DLT. The frequency of targeted toxicities is shown in Table 3. There were 7 events of increased ALT in all courses (6 Grade 1 and 1 Grade 3). Other Grade 3 adverse events were decreased phosphate (1), myelodysplasia (1), decreased hemoglobin (1), decreased leukocytes (1), and decreased neutrophils (1). The half life of pazopanib administered as tablets was approximately 24 hours, which is similar to the half life in adults. One subject with a hepatoblastoma had a PR and 4 subjects had SD for 6 or more months (alveolar soft part sarcoma, osteosarcoma, synovial sarcoma, and myopapillary ependymoma). Parts 2a and 2b of the study are nearing completion of enrollment, but no data are available.

Table 3 Targeted Toxicities in Part 1 of ADVL0815

Toxicity Type	Maximum grade across all courses (total, 101 courses)				
	G1	G2	G3	G4	Total No. Subjects
Left ventricular systolic dysfunction	3	2			5 (22%)
Hypertension	2	9	2		13 (57%)
Proteinuria	9	1	1		11 (48%)
Hypothyroidism	2	3			5 (22%)
Prolonged QTc					0 (0%)

4.6.3. ADVl092X (Planned)

Data from Phase I studies in adults indicate that combination of pazopanib with many cytotoxic or targeted agents results in unacceptable toxicity (primarily hematologic) and identifying tolerable, therapeutic combination regimens has proven difficult. Therefore, pazopanib monotherapy was chosen over combination therapy for studies in pediatric indications. Because single agent antiangiogenic therapy is not likely to be curative, the most appropriate patient population to study pazopanib's therapeutic benefits was considered to be in children who have relapsed after having exhausted all other treatment options.

ADVL092X is a planned open-label, single-arm Phase II trial in partnership with the COG. Pazopanib will be administered as a single agent once daily on a continuous basis at the MTD defined in ADVL0815. Tumor types to be studied will be selected based on

scientific rationale [Dalal, 2005; McGary, 2002; Rowe, 2000; Gerber, 2000]. The primary objective is to determine the therapeutic activity defined by overall response rate and progression free survival, in children with relapsed or refractory sarcomas or neuroblastoma. Six disease strata are being considered for evaluation: 1) rhabdomyosarcoma, 2) non-rhabdomyosarcoma STS, 3) osteosarcoma, 4) Ewing sarcoma and peripheral neuroectodermal tumor, 5) measurable neuroblastoma, and 6) evaluable neuroblastoma. A Simon 2-stage design will be used to assess each disease stratum. It is likely that 10 subjects will be enrolled in each stratum in the first stage and that evidence of activity in at least 2 patients in a stratum will be required to enroll the second stage. No more than 20 subjects will be enrolled in each stratum.

4.6.4. Pazopanib Pediatric Phase III trial (Planned)

Assuming that an acceptable safety profile and sufficient clinical activity is seen in the Phase II trial, ADVL092X, one or more of the strata will be studied in a Phase III trial comparing the clinical activity of pazopanib to physician's choice therapy. Children who have evidence of disease progression following or during standard of care treatment for metastatic disease will be eligible for enrollment. The primary objective will be to assess the effect of pazopanib on overall survival.

4.7. Pediatric Investigation Plan

In 2010 GSK and the EMA agreed to a PIP that includes development of an age appropriate formulation, juvenile toxicity studies, a Phase 1 study to assess safety and determine the MTD of monotherapy (ADVL0815 is expected to fulfill this requirement) , a single arm stratified study to assess efficacy and safety of monotherapy in subjects with STS (ADVL092X is expected to fulfill this requirement) and an open label randomized, active control study of monotherapy to assess safety and efficacy in subjects with STS (the planned Phase III study). The studies of efficacy will be conducted in subjects with RMS, non-RMS STS or Ewing family sarcoma that are recurrent or refractory to standard therapy. It is anticipated that the first efficacy study will be completed in 2016 and the second efficacy study in 2021.

The potential pediatric indication for pazopanib described in the PIP is: Pazopanib is indicated for the treatment of pediatric patients with advanced recurrent soft tissue sarcoma with disease progression following one or more lines of chemotherapy or for whom chemotherapy is not indicated.

4.7.1. Pediatric subsets to be studied in the PIP

Pazopanib (film-coated tablets and oral suspension) will be evaluated in the following pediatric subsets:

- Children (2 to 11 years)
- Adolescents (12 to 18 years)

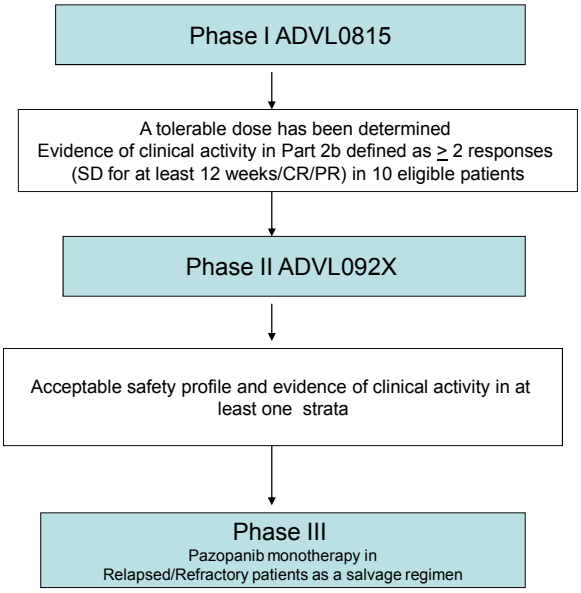
STS (including rhabdomyosarcoma, non-rhabdomyosarcoma and Ewing family sarcoma) occurs in this age range and the risk of pazopanib therapy, based on the pediatric Phase I trial and data from adults appears to be acceptable. The potential for benefit will be

determined by the Phase II and perhaps Phase III trials. A waiver has been requested for newborns and infants below the age of two years due to safety concerns.

4.7.2. Clinical trial plans in the PIP

Pazopanib development in pediatrics agreed to in the PIP is shown in Figure 1. The Phase I and Phase II trials being conducted in collaboration with COG are expected to partially fulfill the obligations of the PIP. The Phase II trial will likely include strata not included in the current PIP.

Figure 1 Clinical plan decision tree



4.8. Post-Marketing Experience in Pediatric Patients

There is no reported post-marketing experience with pazopanib in pediatric patients.

4.9. Challenges in the development of pazopanib for pediatric indications

Four key challenges have influenced the development of pazopanib in pediatrics.

1. In common with development of all medicines in pediatric oncology, the rarity of pediatric cancers and the limited number of subjects for clinical trials have had a major role in determine the best development path. The small number of potential subjects impacts potential endpoints and timelines and limits statistical power to detect a treatment difference. Collaborating with cooperative groups is important in pediatric drug development and GSK has been able to conduct the Phase I trial of pazopanib by working with COG.

2. Because of the role of the VEGF pathway in organ development, pazopanib may have unique toxicities in pediatric patients. For example, effects on post-natal organ development in preclinical models likely preclude the use of pazopanib in patients less than 2 years of age. Inhibition of VEGF signaling also impairs bone growth and tooth development in preclinical models.
3. The need to develop an oral suspension formulation for use in younger children has been challenging because of the bitter taste and poor mouth-feel characteristics of pazopanib powder. Constituents for reconstitution are not always available worldwide, limiting the possibilities for an oral suspension formulation.
4. The inability to safely combine pazopanib with many conventional chemotherapy regimens limits pediatric trials to monotherapy. The focus of pediatric trials is usually on therapies that have the potential to be curative. Single agents rarely have this potential, and anti-angiogenic agents in particular have not been shown to be curative. Thus, single agent pazopanib used as an antiangiogenic agent may be less attractive, compared to other therapies, for pediatric trials when so few subjects are available to participate.

Despite the difficulties inherent in drug development in pediatric oncology and the specific challenges with pazopanib, GSK is committed to its development for children with cancer. The Phase I trial has shown pazopanib to be generally safe when administered to children and has determined the MTD. The Phase II trial will assess efficacy and safety in a number of tumor types and will form the basis of further development.

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